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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
NGUYEN, QUANG	
ART UNIT	PAPER NUMBER
1633	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/500,911	NODA ET AL.	
	Examiner	Art Unit	
	QUANG NGUYEN, Ph.D.	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 November 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,6 and 12-37* is/are pending in the application.

4a) Of the above claim(s) *12-37* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1 and 6* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *11/25/09*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's amendment filed on 11/25/09 was entered.

Claims 1, 6 and 12-37 are pending in the present application.

Claims 12-37 were withdrawn from further consideration because they are directed to non-elected inventions.

Accordingly, amended claims 1 and 6 are examined on the merits herein with the elected tissue factor species.

Remark

The submitted JP 2001-299362 A in the IDS filed on 11/25/2009, without any translation, was considered to the extent of a person who does not have any knowledge in Japanese.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation

under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Amended claims 1 and 6 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rupprecht et al (Kidney International 51:694-702, 1997; IDS) in view of Einstein (WO 01/04356, IDS), Khachigian (WO 01/30394; IDS), Remacle et al (WO 01/73115; IDS filed on 11/25/09) and Erlich et al (Am. J. Pathol. 150:873-880, 1997) . ***This is a new ground of rejection necessitated by Applicant's amendment.***

Ruprecht et al already demonstrated that **Egr-1 induction not only occurs after mitogenic stimulation of mesangial cells (MCs) in culture, but can also be observed with MC proliferation *in vivo* in a rat model of mesangioproliferative glomerulonephritis**; and **a common reaction pattern of various glomerular kidney diseases** such as IgA nephropathy, **diabetic nephropathy**, membranoproliferative glomerulonephritis **is increased proliferation of intrinsic mesangial cells and mesanglial hypercellularity and persistent mesangial hypercellularity together with increased matrix deposition is considered an important factor in progressive glomerular sclerosis and deterioration of renal function** (see at least the abstract and page 694). Ruprecht et al also tested the effect of various anti-sense oligonucleotides directed against Egr-1 by comprising comparing the expression of Egr-1 at both mRNA and protein levels in rat glomerular mesangial cells stimulated with PDGF in the presence or absence of antisense oligonucelotides, and they found that

suppression of Egr-1 mRNA and protein induction interfered with MC mitogenesis (see at least page 699, and Figures 4-6).

Ruprecht et al do not teach specifically a method of screening for a therapeutic substance for a renal disease, including diabetic nephropathy (claim 6), wherein said method comprises steps (a)-(h) as recited in independent claim 1.

At the effective filing date of the present application, Einstein (WO 01/04356) already taught at least **a screening method for identifying modulators (both inhibitors and/or inducers) of Egr-1 (including human Egr-1) induction since an induction of the transcription factor Egr-1 has been observed to induced in tissues isolated from human heart under conditions of ischemia such as coronary artery disease** (see at least Summary of the Invention; page 7, lines 8-10; page 9, lines 3-5; pages 11-15). Einstein also disclosed that **Egr-1 usually functions as an activator of target gene transcription for various genes, including platelet derived growth factor B chain genes** (page 7, line 25 continues to line 2 of page 8); and **Egr-1 recognizes the consensus motif GCG(G/T)GGGCG which is commonly referred to as the GSG motif** (page 8, lines 27-28). Einstein further taught that **the screening method may utilize any available means of monitoring for changes, including down-regulating expression and activity of Egr-1; and cells or transduced or transfected cell lines would be contacted with agents under appropriate conditions, and the proteins from "agent contacted" cells and control, non-agent contacted cells would be compared for changes in the expression and/or activity of Egr-1 such as the ability of Egr-1 to bind to a GSG**

consensus containing nucleic acid molecule (see at least page 14, line 27 continues to line 3 of page 16; and page 17, lines 10-30).

Additionally, Khachigian (WO 01/30394) also taught **a screening method for agents which decreases expression, nuclear accumulation and/or activity of Egr-1, including human Egr-1, since Egr-1 is critical in vascular endothelial cell replication and replication and therefor such agents would be useful for cancer treatment via their ability to inhibit angiogenesis** (see at least Summary of the Invention; page 15, lines 20-29 and Table 1). Khachigian disclosed that the putative agents may be tested by any suitable means known to those skilled in the art (page 15, lines 20-29). Khachigian further disclosed that **Egr-1 binds to the promoters of a spectrum of genes including tissue factor and PDGF-B genes** (page 1, line 34 continues to line 6 of page 2).

Neither the screening methods of Einstein and Khachigian teaches specifically the steps of immobilizing on a solid phase a polynucleotide to which a cell lysate containing the protein or salt thereof comprising the amino acid sequence of SEQ ID NO:2 (human Egr-1) and selecting a tested compound that decreases the level of at least tissue factor (elected species).

However, at the effective filing date of the present application Remacle et al already disclosed **a method for screening, detecting and quantitating one or more transcriptional factor(s), including Egr-1, present in a cell or a cell lysate** (including a nuclear lysate of a cell), **said method comprises the steps of: (a) binding to an insoluble solid support, double-stranded DNA sequence(s) comprising a specific**

nucleotide sequence able to bind specifically the transcriptional factor(s); (b) putting into contact the transcriptional factor(s) with the bound double-stranded DNA sequences(s); and (c) identifying and/or quantifying a signal resulting from the binding of the transcriptional factor(s) to the double-stranded DNA sequence(s); wherein the signal is obtained using a non-radioactive detection means utilizing primary antibody raised against the transcriptional factor(s) and a secondary labeled antibody directed against the primary antibody (see at least paragraphs 20-24, 29-31, 40-42; Fig. 1 and Table 1 on page 29). Remacle et al further disclose that **the non-radioactive method is rapid, more sensitive than gel retardation, and suits for large-scale screening or detection upon various solid supports** (paragraphs 21, 24 and 29).

Erlich et al also taught that **increased glomerular tissue factor (TF) expression is associated with glomerular fibrin deposition and renal failure in human and experimental crescentic glomerulonephritis**, and demonstrated that **TF is the major *in vivo* initiator of fibrin deposition in crescentic glomerulonephritis** (see at least the abstract).

Accordingly, it would have been obvious for an ordinary skilled artisan to modify the teachings of Ruprecht et al. by also establishing a screening method for an agent or a compound/substance that decreases the production of a protein or a salt thereof comprising SEQ ID NO:2 (human Egr-1) and/or decreases the binding activity of said protein or salt thereof (for examples agents or compounds other than the disclosed anti-sense oligonucleotides directed against Egr-1), and the screening method comprises

the steps of immobilizing on a solid phase a polynucleotide to which a cell lysate containing the human Erg-1 is binding to; and selecting for the compound/substance that decreases the expression level of human Egr-1 which is also known to regulates the tissue factor gene, including the use of human glomerular mesangial cells in such a screening assay, in light of the teachings of Einstein (WO 01/04356), Khachigian (WO 01/30394), Remacle et al and Erlich et al. as discussed above.

An ordinary skilled artisan would have been motivated to carry out the above modifications because: (1) screening methods for identifying modulators/inhibitors of Egr-1 expression and/or activity have been successfully taught by both Einstein (WO 01/04356), Khachigian (WO 01/30394) for treating coronary artery disease and cancer, respectively; (2) the non-radioactive method of Remacle et al for detecting and quantitating one or more transcriptional factor(s), including Egr-1, present in a cell or a cell lysate would be desirable and selected by an ordinary skilled artisan because it is rapid, more sensitive than gel retardation, and suits for large-scale screening or detection; and (3) an ordinary skilled artisan would also select for an agent that decreases the level of tissue factor (e.g., an agent that suppresses human erg-1 expression) since Erlich et al already taught at least that increased glomerular tissue factor (TF) expression is associated with glomerular fibrin deposition and renal failure in human and experimental crescentic glomerulonephritis. Additionally, it is further noted that Egr-1 is known to bind to the promoter of tissue factor gene as taught by Khachigian.

An ordinary skilled artisan would have a reasonable expectation of success in light of the teachings of Ruprecht et al., Einstein (WO 01/04356), Khachigian (WO 01/30394), Remacle et al. and Erlich et al., coupled with a high level of skill of an ordinary skilled artisan in the relevant art.

Therefore, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Response to Arguments

Applicants' arguments related to the above rejection in the Amendment filed on 11/25/09 (pages 9-13) have been fully considered but they are respectfully not found persuasive for the reasons discussed below.

Applicants argue that McKay does not teach the step of "lysing the cell to obtain a cell lysate containing the protein or salt thereof as recited in amended claims; and this defect is not remedied by Rupprecht, Einstein, Khachigian and Erlich alone or in combination. With respect to the Rupprecht reference, Applicants argue that this reference does not measure the binding activity of Egr-1 in the same Western blotting assay that was used to measure the Egr-1 protein expression. With respect to the Einstein reference, Applicants argue that the reference does not discuss assaying the production of the protein in the disclosed screening method. With respect to the Khachigian reference, Applicants also argue that the reference teaches measuring protein production and binding assay in separate assays. With respect to the Ehrlich reference, the reference is silent regarding to Egr-1 and therefore it does not teach or

suggest "measuring production of the protein or salt thereof and the binding activity of the protein or salt thereof to the polynucleotide" in a single assay.

First, Applicant's arguments related to the McKay reference are moot in light of the above new ground of rejection necessitated by Applicant's amendment, specifically the limitation "lysing the cell to obtain a cell lysae containing the protein or salt thereof" and "contacting the solid phase with the cell lysate and an antibody against the protein or salt thereof".

Second, it appears that Applicants considered each of the teachings of Rupprecht, Einstein, Khachigian and Ehrlich in total isolation one from the others. At the effective filing date of the present application, screening **methods for identifying modulators/inhibitors of Egr-1 expression and/or activity have been successfully taught by both Einstein (WO 01/04356), Khachigian (WO 01/30394) for treating various diseases such as coronary artery disease and cancer**. **Egr-1 recognizes the consensus motif GCG(G/T)GGGCG** which is commonly referred to as the GSG motif; and **it binds to the promoters of a spectrum of genes including tissue factor and PDGF-B genes**. Moreover, Erlich et al also taught that **increased glomerular tissue factor (TF) expression is associated with glomerular fibrin deposition and renal failure in human and experimental crescentic glomerulonephritis**, and demonstrated that **TF is the major *in vivo* initiator of fibrin deposition in crescentic glomerulonephritis**. More importantly, Ruprecht et al demonstrated that **Egr-1 induction not only occurs after mitogenic stimulation of mesangial cells (MCs) in culture, but can also be observed with MC proliferation *in vivo* in a rat model of**

mesangioproliferative glomerulonephritis; and **a common reaction pattern of various glomerular kidney diseases** such as **diabetic nephropathy**, membranoproliferative glomerulonephritis **is increased proliferation of intrinsic mesangial cells and mesanglial hypercellularity and persistent mesangial hypercellularity together with increased matrix deposition is considered an important factor in progressive glomerular sclerosis and deterioration of renal function.** Finally, at the effective filing date of the present application Remacle et al also disclosed **a rapid, sensitive, non-radioactive method for screening, detecting and quantitating one or more transcriptional factor(s), including Egr-1, present in a cell or a cell lysate** (including a nuclear lysate of a cell), **said method comprises the steps of: (a) binding to an insoluble solid support, double-stranded DNA sequence(s) comprising a specific nucleotide sequence able to bind specifically the transcriptional factor(s); (b) putting into contact the transcriptional factor(s) with the bound double-stranded DNA sequences(s); and (c) identifying and/or quantifying a signal resulting from the binding of the transcriptional factor(s) to the double-stranded DNA sequence(s); wherein the signal is obtained using a non-radioactive detection means utilizing primary antibody raised against the transcriptional factor(s) and a secondary labeled antibody directed against the primary antibody**. Accordingly, it would have been obvious for an ordinary skilled artisan to combine the teachings of Ruprecht et al., Einstein (WO 01/04356), Khachigian (WO 01/30394), Remacle et al. and Erlich et al. in the manner set forth above for the stated motivations to arrive at the presently claimed invention.

Third, the rapid, sensitive, non-radioactive assay method of Remacle et al for quantitating one or more transcriptional factors, including Egr-1, **is capable for measuring both the amount as well as the binding activity of the transcriptional factor Egr-1 because the assay requires at least Egr-1 binds to a GSG motif to be detected and/or quantitated**.

Conclusion

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Quang Nguyen, Ph.D., whose telephone number is (571) 272-0776.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's SPE, Joseph T. Woitach, Ph.D., may be reached at (571) 272-0739.

To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1633; Central Fax No. (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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/QUANG NGUYEN/

Primary Examiner, Art Unit 1633